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Case Series

Fluocinolone acetonide intravitreal implant (Retisert®) in the treatment of sight threatening macular oedema of juvenile idiopathic arthritis-related uveitis

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ABSTRACT.

Purpose: **We describe eight patients with juvenile idiopathic arthritis-related chronic uveitis, who received a fluocinolone acetonide implant (FAI, Retisert®, Bausch&Lomb) in one eye. All patients had poor visual acuity (VA) due to persistent macular oedema in one or both eyes despite treatment with antirheumatic medication.**

Methods: **Median age of the patients was 22.9 years (range, 14.1–39.7) and duration of uveitis 13.0 years (range, 6.8–28.4) at FAI implantation. Median preoperative best-corrected visual acuity (BCVA) was 0.1 (range, 0.05–0.4) and Standardization of Uveitis Nomenclature, SUN-grade was SUN 2+ (range, 0.5–4.0). All patients had been treated extensively with systemic corticosteroids and antirheumatic drugs by the time of FAI implantation. The median follow-up time was 5.3 years (range, 4.4–6.3).**

Results: **Macular edema resolved in a median time of 0.2 years (range, 0.04–0.39) after the FAI implantation. The median BCVA was 0.5–0.63 (range, 0.1–1.0) from 1 to 5 years of follow-up. Macular edema did not recur in 5 eyes after the implantation. In three eyes, the macular oedema relapsed at 2.7, 2.9 and 5.5 years of follow-up. All our patients needed antirheumatic drugs in addition to the FAI to treat their macular edema. During the follow-up, 7 eyes required further intraocular operations: 4 cataract operations, 4 intraocular pressure -lowering operations and 1 retinal detachment surgery were performed.**

Conclusion: **Fluocinolone acetonide implant is a valuable option in the treatment of persistent macular edema associated with JIA-related uveitis refractory to systemic treatments.**

Key words: uveitis – juvenile idiopathic arthritis – macular edema – fluocinolone acetonide implant

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Introduction

Persistent macular oedema is the most common cause of visual impairment in chronic uveitis (Tomkins-Netzer et al. 2014). Macular oedema occurs in up to 15% of patients with juvenile idiopathic arthritis (JIA)-related uveitis (Angeles-Han et al. 2015; de Boer et al. 2015). In JIA-related uveitis, it associates with vision loss (de Boer et al. 2015) and legal blindness (Angeles-Han et al. 2015). Macular oedema is more common among patients with longer duration of uveitis (de Boer et al. 2015). There is no drug of choice to treat macular oedema associated with JIA uveitis. Potentially effective antirheumatic drugs include cyclosporine, infliximab and adalimumab (Diaz-Llopis et al. 2008; Pato et al. 2011; Heiligenhaus et al. 2012; García-De-Vicuña et al. 2013). Intravitreal corticosteroids have been used successfully in treating paediatric uveitic macular oedema (Sallam et al. 2008; Sella et al. 2015). Sustained release intravitreal corticosteroid implants have been suggested for uveitic macular oedema when systemic antirheumatic therapy fails (Foster et al. 2016). Fluocinolone acetonide implant (FAI, Retisert®, Bausch & Lomb) has been shown to effectively control inflammation and macular oedema in eyes with uveitis (Kempen et al. 2015).

We describe eight JIA-related uveitis patients with sight-threatening chronic macular oedema resistant to disease-modifying antirheumatic drugs (DMARDs), biologic drugs and systemic corticosteroids. Periocular and intravitreal corticosteroid were given to two patients prior FAI implantation. Fluocinolone acetonide implantation was performed in eight eyes with favourable results.

Patients and Methods

Nine fluocinolone acetonide implants were implanted in 2010–2012 in Helsinki University Hospital, Department of Ophthalmology to treat persistent macular oedema in JIA-related uveitis. Eight patients with eight FAI implanted eyes were included in the analysis after one patient dropped from the follow-up after a good initial response to FAI. Despite treatment with topical and systemic (eight patients), periocular (1), intravitreal corticosteroids (1 dexamethasone implant), DMARDs (8) and biologic drugs (8), all patients had developed resistant sight-threatening macular oedema. FAI implantation remained the last effort. Four eyes were phakic and four pseudophakic. Two eyes had been diagnosed with secondary glaucoma and one had had IOP-lowering surgery prior to the FAI implantation. FAI was implanted via pars plana in one eye of each patient. One patient had a more extensive vitreoretinal operation in addition to FAI implantation due to grave epiretinal membrane formation. All patients were followed up every 1–12 weeks. Corticosteroid and antirheumatic medications were moderated pre- and postoperatively according to the activity of uveitis and arthritis in cooperation with rheumatologists. The ethics committee of the Helsinki University Hospital approved this study, and its design complies with the Declaration of Helsinki.

The following data were recorded: age at onset of uveitis, age at onset of JIA diagnosed by a paediatric rheumatologist, antirheumatic medication, best-corrected visual acuity in decimal notations (BCVA) and uveitis activity in Standardization of Uveitis Nomenclature (SUN) grading (Jabs et al. 2005) preoperatively and during the follow-up, ocular complications and intraocular operations. (OCT) was used to detect the macular oedema. Due to media opacities and pupillary abnormalities in these uveitis eyes, resolution of the images was not high enough for standard progression analysis. The Statistical Package for the Social Sciences SPSS 19 (IBM Corp., NY) was used. All tests were two-sided, and $p < 0.05$ was considered significant.

Results

A fluocinolone acetonide intravitreal implant was implanted in one eye of eight JIA-uveitis patients. (Table 1) The median age was 22.9 years (range, 14.1–39.7) and duration of uveitis 13.0 years (range, 6.8–28.4) at the time of implantation.

Six patients had been diagnosed with uveitis at their first ophthalmological screening (Papadopoulou et al. 2017). Two patients were diagnosed with paediatric anterior uveitis at 13.9 and 7.3 years of age and later with idiopathic arthritis. According to EULAR criteria (Wood 1978), five patients had juvenile idiopathic oligoarthritis, three patients had juvenile idiopathic polyarthritis and one patient was diagnosed with juvenile spondyloarthritis.

The median preoperative BCVA was 0.1 (range, 0.05–0.4), and the median SUN grade was SUN 2+ (range, 0.5–4.0) in the treated eye. The uveitis was unilateral in two and bilateral in six patients. Bilateral macular oedema was present in three patients (BCVA ≤0.1 bilaterally) preoperatively. Preoperative BCVA of the fellow eye was 1.0 in five patients. The median follow-up was 5.0 years; range, 3.5–6.0.

Macular oedema resolved in a median time of 0.2 years (range, 0.04–0.39) in the treated eyes (Figure 1). The median BCVA was 0.5–0.63 from 1 to 5 years of follow-up (Table 2, Figure 2). In three eyes, macular oedema relapsed at 2.7, 2.9 and 5.5 years after the FAI implantation. The relapses were resolved with changes in antirheumatic medication in two and with a dexamethasone implant in one patient. Besides three anterior segment activations of three eyes (at 2.9, 3.1 and 4.7 years), all treated eyes stayed ≤SUN 1+ during the follow-up.

In the six patients with binocular uveitis, five patients had at least one eye ≥0.63 at the end of the follow-up. (BCVA) was ≤0.16 binocularly in one patient due to macular scarring.

At the last follow-up, six patients were treated with topical corticosteroids, one with systemic corticosteroids, six patients were on DMARDs and five needed biologic drugs to treat their uveitis, arthritis or both.

Four eyes had had a cataract operation before and cataract was operated on in the remaining four eyes 0.5–1.2 years after FAI implantation.

Two eyes had been diagnosed with secondary glaucoma prior the FAI implantation. The median preoperative IOP was 10 mmHg (range, 8–20). The IOP of two eyes has stayed ≤21 mmHg during the follow-up. The IOP of six eyes rose to >21 mmHg at 0.5–4.7 years of follow-up (Figure 3). The IOP of two of these eyes has stayed ≤26 mmHg with antiglaucomatous medication and without IOP-lowering surgeries. Four eyes had IOP ≥30 mmHg on maximal tolerated antiglaucomatous medication and were operated on 0.3–2.2 years after the initial IOP rise >21 mmHg, 0.9–5.2 years after the FAI implantation. One of these eyes had secondary glaucoma prior the FAI implantation. One trabeculectomy, one deep sclerectomy and two drainage implant surgeries were performed. By the end of the follow-up, one of these eyes was on antiglaucomatous medication, and no additional IOP-lowering surgeries had been performed. Retinal detachment occurred in one eye that had had epiretinal membrane peeling in addition to FAI implantation. The eye was operated on successfully one month after FAI implantation. No implants were removed, and no dissociation of FAIs has been noticed to date.

Discussion

Macular oedema is a sight-threatening complication of JIA uveitis (Tomkins-Netzer et al. 2014; Angeles-Han et al. 2015; de Boer et al. 2015). It is more

Table 1. Characteristics of the eight patients.

	Median	Range
Age at the onset of uveitis (years)	8.3	3.1–14.1
Age at operation (years)	22.9	14.1–39.7
Duration of uveitis at operation (years)	13.0	6.8–28.4
Preoperative BCVA	0.1	0.05–0.4
Preoperative SUN grade	2.0	0.5–4.0

BCVA = best-corrected visual acuity; SUN = standardization of uveitis nomenclature.

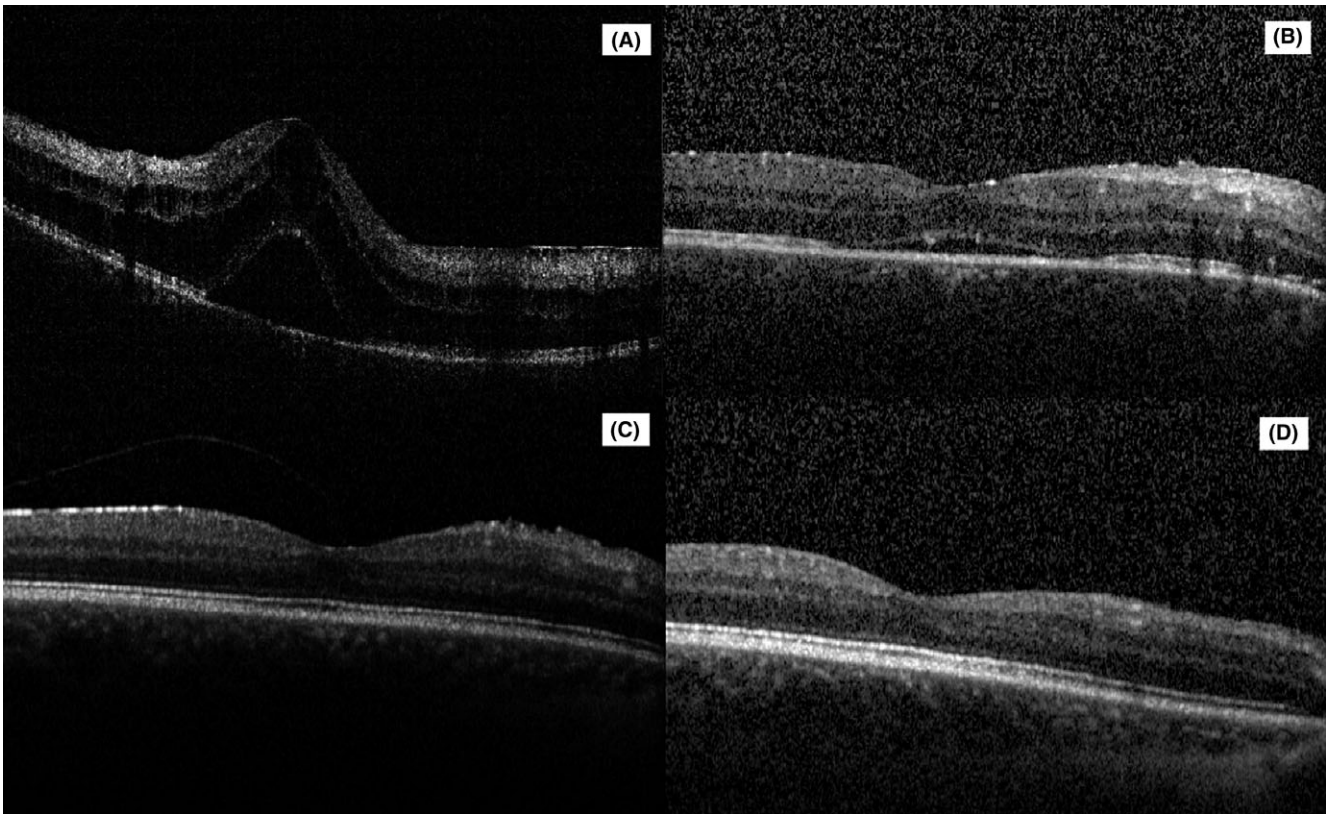

Fig. 1. OCT images prior to the fluocinolone acetonide implant operation (A), 2 weeks (B), 2 years (C) and 5 years (D) after the operation.

Table 2. Best-corrected visual acuity in decimal notation of the fluocinolone acetonide implant eyes preoperatively and at 1–5 years of follow-up.

	No of eyes	Median BCVA	Range	p value*
Preoperative	8	0.10	0.05–0.4	
At 1 year	8	0.50	0.1–1.0	0.018*
At 2 years	8	0.56	0.16–1.0	0.012*
At 3 years	8	0.56	0.16–1.0	0.018*
At 4 years	8	0.52	0.125–1.0	0.018*
At 5 years	7	0.63	0.32–0.7	0.018*

BCVA = Best-corrected visual acuity.
* Wilcoxon signed-ranks test for the improvement from the preoperative BCVA.

common in patients with longer duration of uveitis (de Boer et al. 2015), like in our patients who had had uveitis for a median time of 13.0 years.

For treating uveitic macular oedema, corticosteroids and antirheumatic drugs are potentially effective (Pato et al. 2011). Intravitreal corticosteroids have been used to resolve macular oedema in uveitis balancing the potential benefits against the high complication risks (Sallam et al. 2008; Arcinue et al. 2013; Sella et al. 2015). When antirheumatic treatment proved to be insufficient in treating the chronic macular oedema of our JIA-uveitis patients, intravitreal fluocinolone implant remained the last option.

Persistent macular oedema was resolved with a fluocinolone acetonide implant in all eight eyes of eight patients with JIA-related uveitis. Three patients' macular oedema relapsed during the follow-up. Similar results have been reported in the MUST trial where about two-thirds of eyes with uveitic macular oedema due to intermediate or posterior uveitis improved with a FAI. In the MUST trial, FAI and systemic antirheumatic treatment were as effective in a follow-up up to 4.5 years (Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group et al. 2015). All our patients needed disease-modifying and biologic antirheumatic drugs in addition to the FAI to treat their macular oedema. Only two patients did not need antirheumatic therapy by the last follow-up.

Postoperative FAI complications are frequent (Foster et al. 2016; Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group et al. 2015, Arcinue et al. 2013; Sen et al. 2016). All phakic patients underwent a cataract operation postimplantation in our study. Our young patient group had a high rate (four of eight patients) of IOP-lowering surgeries. Young age at implantation has been associated with IOP rise after the FAI implantation (Parekh et al. 2015). The success rate of the four IOP-lowering surgeries in our study was high: no reoperations were performed and only one patient needed antiglaucomatous medication by the last follow-up. One retinal detachment was operated on successfully in one eye that had undergone epiretinal membrane peeling in addition to FAI implantation. Despite the complications and relapses, the improvement in (VA) was maintained until the last follow-up in all our patients.

In a study by Arcinue et al., no significant differences were seen in visual acuity or inflammation after a

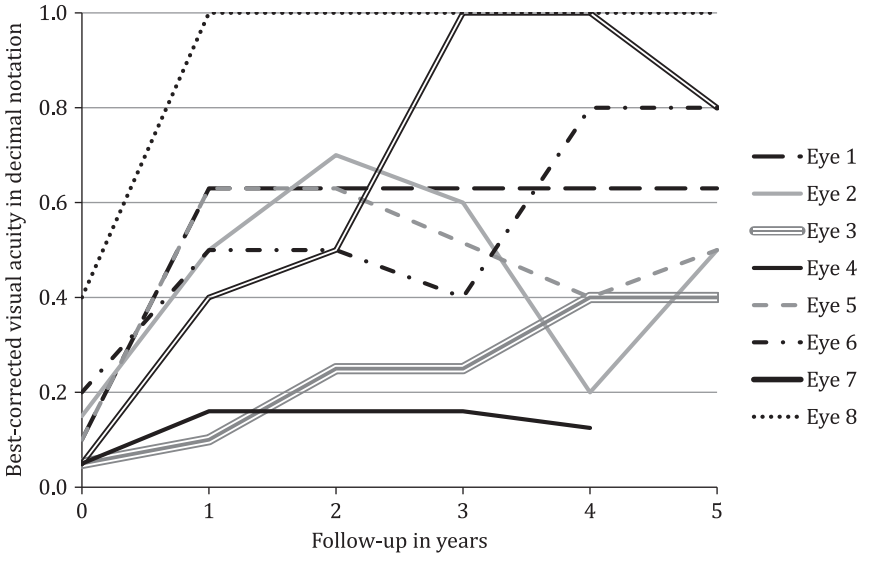

Fig. 2. Visual acuity in decimal notation of eight patients at implantation and at 1–5 years of follow-up. Macular oedema relapsed in eyes numbered 2, 5 and 6.

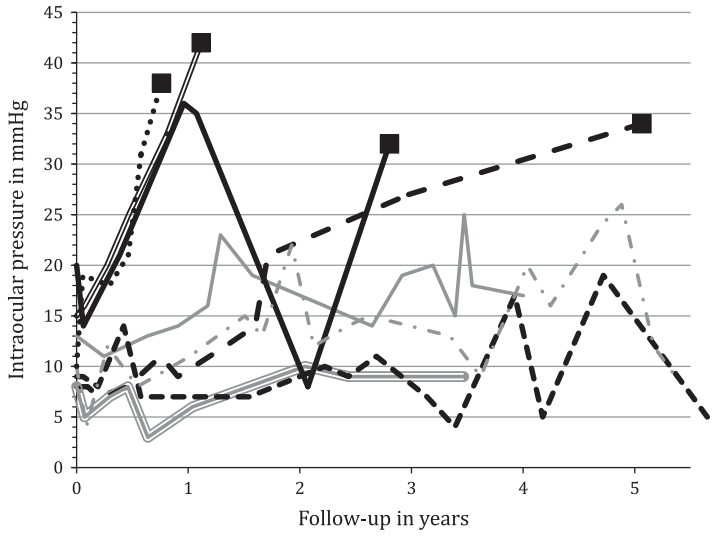

Fig. 3. Intraocular pressure (mmHg) until an intraocular pressure lowering operation marked with ■ or last follow-up of intraocular pressure.

sustained release intravitreal dexamethasone implant compared with fluocinolone implant in panuveitis eyes. Higher rates of complications and longer survival time for a second implant were found among the FAI eyes (Arcinue et al. 2013). Prior the FAI implantation, only one of our patients was treated with a sustained release intravitreal dexamethasone implant with which the macular oedema did not resolve.

In our experience, intravitreal fluocinolone acetonide implants can be considered a last resort treatment for JIA-uveitis patients with poor vision due to macular oedema that is resistant to systemic corticosteroids and antirheumatic treatment. Because of the potential FAI-related complications, close monitoring of the implanted eyes is needed for years after the implantation.

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